2. The specification was objected to for containing two typographical errors on pages 25 and 40.

3. Claims 6-8 were rejected under 35 U.S.C. 103(a) as being unpatentable over Graham *et al.* (U.S. Patent 6,127,120) in view of Cook *et al.* (U.S. Patent 6,127,533) and Fodor *et al.* (U.S. Patent 5,800,992).

4. Claims 9-17 were rejected under 35 U.S.C. 103(a) as being unpatentable over Graham *et al.* (U.S. Patent 6,127,120) in view of Cook *et al.* (U.S. Patent 6,127,533), Hacia *et al.* (U.S. Patent 6,013,449), McGall *et al.* (U.S. Patent 6,156,501) and Fodor *et al.* (U.S. Patent 5,800,992).

5. No claims were allowed.

Response to the rejections under 35 U.S.C. 103

Claims 6-8 were rejected under 35 U.S.C. 103 purportedly because the claimed invention is not patentable over Graham *et al.* (U.S. Patent 6,127,120) in view of Cook *et al.* (U.S. Patent 6,127,533) and Fodor *et al.* (U.S. Patent 5,800,992). These claims have been cancelled an rewritten as claims 26-29 to correct the dependency of the independent claims and provide the feature that the reusable array be resistant to acid solutions of pH 1-2. Applicant respectfully submits that the amended claims disclose a method of identifying differences in nucleotide sequences using a reusable array of modified oligonucleotides that is neither suggested nor disclosed in the cited references.

As mentioned above, Applicant has amended the claims to provide the feature that the reusable array is stripped of hybridized nucleic acids between steps or between experiments by washing with an acidic solution of pH 1-2 (*i.e.*, conditions under which the nucleic acids are protonated). In contrast, Fodor *et al.* discloses that a matrix substrate may be reused by treating it with organic or inorganic solvents to which the substrate, the nucleic acid molecules, and their linkages are inert (column 25, lines 4-15). This reference discloses further that substrate reuse should employ mild conditions and neutral pH if recycling is desired (column 56, lines 2-7), thereby teaching away from a critical feature of the claimed method (*i.e.*, incubation in acid solution at pH 1-2).

In a similar manner, Graham *et al.* discloses that the array can be prepared for reuse by removal of mRNA by treatment with RNase or alkali (column 31, lines 60-66). Applicants submit that the disclosure of basic or enzymatic washing conditions by Graham *et al.* also clearly teaches away from the claimed method wherein strongly acidic washing conditions are employed to remove the hybridized nucleic acids from the array. Applicant submits that in the absence of either Fodor *et al.* or Graham *et al.* there is no motivation in the remaining cited reference (Cook *et al.*) to modify their teachings to produce the claimed invention. Applicant further submits that none of the cited references, either alone or in

combination, teach or suggest all of the features of the claimed methods for identifying nucleic acid sequence differences between target and reference molecules using highly acid-resistant reusable oligonucleotide arrays, nor do they render Applicant's claimed method obvious.

Claims 9-17 were also rejected under 35 U.S.C. 103 purportedly because the claimed invention is not patentable over Graham *et al.* (U.S. Patent 6,127,120) in view of Cook *et al.* (U.S. Patent 6,127,533), Hacia *et al.* (U.S. Patent 6,013,449), McGall *et al.* (U.S. Patent 6,156,501) and Fodor *et al.* (U.S. Patent 5,800,992). These claims have also been cancelled and rewritten as claims 18-25 to correct the dependency of the independent claims and also to provide the feature that the reusable array is resistant to acid solutions of pH 1-2. Applicant respectfully submits that the amended claims disclose a method of detecting nucleotide sequences in two or more separate collections of nucleic acid molecules, hybridized separately, in a single experiment using a reusable array of modified nucleic acid molecules that is neither suggested nor disclosed in the cited references. Applicant submits that Fodor *et al.* and Graham *et al.* do not suggest or teach all the limitations of the claimed method for the same reasons as discussed above, and that, in the absence of these references, none of the remaining cited references are applicable.

In addition, neither Hacia *et al.* nor McGall *et al.* disclose or suggest incubating an oligonucleotide array with an acid solution of pH 1-2, a limitation of the claimed method. The Office Action indicates that McGall *et al.* discloses oligonucleotides modified to contain 7-deazaadenine and 7-deazaguanine to stabilize oligonucleotide arrays toward acidic conditions. This reference, however, does not disclose that these modifications to the oligonucleotides on the array will render them resistant to nuclease degradation, a limitation of the modified oligonucleotides utilized in the claimed method. With regard to Hacia *et al.*, Applicant brings to the attention of the Examiner that the method of claim 18 is directed to a hybridization of a first-labeled nucleic molecule to an array, removal of the first labeled nucleic acid the array using acidic conditions, followed by hybridization of a second-labeled nucleic acid molecule. Hacia *et al.* discloses that the reference and the test agents are co-hybridized to the array (column 13, line 37) and does not disclose individual steps where each of the nucleic acids are hybridized to the array sequentially. Applicant respectfully submits that none of the cited referenced are applicable in light of the claim amendments and that the cited references cannot properly be combined to create a *prima facie* case of obviousness.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, he is invited to telephone the undersigned at his convenience.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned Version with markings to show changes made.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
Morgan, Lewis & Bockius LLP

Dated: August 6, 2002
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The specification on page 25, lines 11-25 has been amended as follows:

Oligonucleotides having a sequence unique to that gene are [~~preferabl[;]y~~] preferably used in the present invention. Different methods may be employed to choose the specific region of the gene to be targeted. A rational design approach may also be employed to choose the optimal oligonucleotide sequence for the hybridization array. Preferably, the region of the gene that is selected is chosen based on the following criteria. First, the sequence that is chosen should yield a oligonucleotide composition that preferably does not cross-hybridize with any other oligonucleotide composition present on the array. Second, the sequence should be chosen such that the oligonucleotide composition has a low probability of cross-hybridizing with an oligonucleotide having a nucleotide sequence found in any other gene, whether or not the gene is to be represented on the array from the same species of origin, e.g., for a human array, the sequence will not be present in any other human genes. As such, sequences that are avoided include those found in: highly expressed gene products, structural RNAs, repeated sequences found in the sample to be tested with the array and sequences found in vectors. A further consideration is to select sequences that provide for minimal or no secondary structure, structure which allows for optimal hybridization but low non-specific binding, equal or similar thermal stabilities, and optimal hybridization characteristics.

The specification on page 39, line 24 to page 40, line 4 has been amended as follows:

The stability of duplexes having 2'-substituted nucleotides versus duplexes without such modification was tested by examining the T_m of these complexes. 4 μM each of 20-mer oligonucleotide (5'- ggt ggt tcc tcc tca gtc gg -3'; SEQ ID NO: 1) and its complement (5'- ccg act gag aag gaa cca cc -3'; **SEQ ID NO: 2**) were bound in a solution of 50 mM NaCl, 10 mM PO_4 buffer, pH 7.4. Each of the nucleotides of the oligonucleotide had the same 2' group. Following binding, the melting temperature was determined as described. (See L.L.Cummins et al. Nucleic Acids Research 23:2019-2024 (1995).)